PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 7/06, 31/54, 31/40

A1

(11) International Publication Number: WO 88/ 00040

(43) International Publication Date: 14 January 1988 (14.01.88)

(21) International Application Number: PCT/US87/01575

(22) International Filing Date: 2 July 1987 (02.07.87)

(31) Priority Application Numbers:
881,233
883,671
883,681
883,679
883,678
883,680
883,682
883,683
004,455
004,457
004,458
004,459
004,460
004,461
004,462

(32) Priority Dates:
2 July 1986 (02.07.86)
9 July 1986 (09.07.86)
9 July 1986 (09.07.86)
9 July 1986 (09.07.86)
9 July 1986 (09.07.86)
9 July 1986 (09.07.86)
9 July 1986 (09.07.86)
9 July 1986 (09.07.86)
9 July 1986 (09.07.86)
20 January 1987 (20.01.87)
20 January 1987 (20.01.87)
20 January 1987 (20.01.87)
20 January 1987 (20.01.87)
20 January 1987 (20.01.87)
20 January 1987 (20.01.87)
20 January 1987 (20.01.87)

(33) Priority Country: US

(71) Applicant: AMERICAN HEALTH PRODUCTS CORPORATION [US/US]; 200 South Biscayne Boulevard, Miami, FL 33131 (US).

(72) Inventors: FROST, Phillip ; 200 South Biscayne Boulevard, Miami, FL 33131 (US). FISHMAN, Jack ; 876 Park Avenue, New York, NY 10028 (US).

(74) Agents: WEGNER, Harold, C. et al.; Wegner & Bretschneider, P.O. Box 18218, Washington, DC 20036 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent).

Published
With international search report.

(54) Title: TOPICAL HAIR GROWING COMPOSITION AND KIT

(57) Abstract

A method for enhancing growth of fine vellous hair into terminal hair in an at least partially bald person which comprises topically applying to the scalp a compound selected from the group consisting of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide, 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3,4-dihydro-2-methyl-3-[[(2,2,2-trifluoroethyl)thio]methyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide whereby the smooth muscles in the small blood vessels in the papilla part of connective tissue of skin that supplies the hair follicle is relaxed, thereby increasing blood flow to the hair matrix leading to the maturation of fine hairs into terminal hairs. Also provided is a topical medication and method for reversing the effects of baldness focused upon said compound as the active ingredient. A kit is provided which comprises the medication with said compound suitable for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises a package including said compound and directions for administration of said compound to said scalp for the reversal of the effects of baldness.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**ML**	Mali
AU	Australia	**GA**	Gabon	**MR**	Mauritania
BB	Barbados	**GB**	United Kingdom	**MW**	Malawi
BE	Belgium	**HU**	Hungary	**NL**	Netherlands
BG	Bulgaria	**IT**	Italy	**NO**	Norway
BJ	Benin	**JP**	Japan	**RO**	Romania
BR	Brazil	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SN**	Senegal
CH	Switzerland	**LI**	Liechtenstein	**SU**	Soviet Union
CM	Cameroon	**LK**	Sri Lanka	**TD**	Chad
DE	Germany, Federal Republic of	**LU**	Luxembourg	**TG**	Togo
DK	Denmark	**MC**	Monaco	**US**	United States of America
FI	Finland	**MG**	Madagascar		

Topical hair growing composition and kit.

In accordance with a first aspect of the invention there is provided A method of enhancing growth of fine vellous hair into terminal hair in an least partially bald person which comprises topically applying to the scalp a compound selected from the group consisting of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide, 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide whereby the smooth muscles in the small blood vessels in the papilla part of connective tissue of skin that supplies the hair follicle is relaxed, thereby increasing blood flow to the hair matrix leading to the maturation of fine hairs into terminal hairs. Thus, the method provides permitting the normal growth of fine vellous hair into terminal hair. According to this aspect of the invention, in one embodiment there is provided a method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 1, wherein said compound is applied from a topical solution containing at least about 0.01 weight percent said compound in a suitable carrier for said compound.

The total amount of said compound applied each day to the scalp of the patient will vary dependent upon the individual patient. It is contemplated that said compound is administered at least once per day, with one embodiment being twice per day application. The concentration of said compound

is also not critical as it is the total amount of said compound that is important. The suitable solvent serves to place said compound in contact with the bald area, so that ultimately there is only the said compound acting directly on the site to the effected. Because the dosage is topical, essentially 100% of said compound is in direct contact with the area to be treated, so that very low dosages can be used.

In a preferred embodiment the individual dosage will be from about 0.5 to about 2 cc, once or twice per day, at any of the concentration ranges.

In one embodiment of this first aspect of the present invention there is provided a topical solution containing at least about 0.01 weight percent said compound in a suitable carrier for said compound. The total amount of said compound in the suitable carrier may vary greatly, it being understood that it is the total dosage of said compound that is important, and not the total amount of the total solution. To the extent that it is desired not to have too great an amount of said compound applied to any one spot on the scalp, a more dilute solution is preferred so that a larger total volume of fluid is applied to the scalp. The maximum amount of said compound is widely varied and said compound may be present up to the saturation point in the suitable solvent. One preferred embodiment is the provision of at least about 0.01% said compound.

In a preferred embodiment of this first aspect of the present invention, said suitable carrier is propylene glycol. In yet another preferred embodiment, said suitable carrier is an ethanolic solution.

In a second aspect of the present invention, there is provided a topical medication for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises a baldness-reversing amount of said compound in a form suitable for topical administration in a carrier

therefor, said compound upon continued application to said scalp effecting the growth of hair thereon. In said topical medication said compound is in one embodiment present in an amount of at least about 0.01 weight percent said compound in said suitable carrier for said compound.

In a third aspect of the present invention there is provided a method for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises administering topically to said scalp a baldness-reversing amount of said compound, said compound upon continued application to said scalp effecting the growth of hair thereon. In a preferred embodiment of said method, said compound is applied from a topical solution containing at least about 0.01 weight percent compound in a suitable carrier for said compound.

In a fourth aspect of the present invention there is provided a kit containing a medication suitable for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises a package containing:

(a) a container including said compound in a form suitable for topical administration to the scalp of said subject; and

(b) directions for administration of said compound to said scalp for the reversal of the effects of baldness

said compound upon continued application to said scalp effecting the growth of hair thereon. The container may be a standard pharmaceutical container such as a bottle with label directions attached directly to the bottle which explain that said compound which is the active ingredient of the present kit, topical medication and method, is to be topically administered to the scalp of an at least partially bald patient wishing to have hair growth in the bald areas of his

scalp. Alternatively, the container may be a box or other cardboard, plastic or similar container having therein both a package insert with instructions on how to use said compound as a topical baldness treatment together with an inner container of said compound in a suitable solvent therefor.

Baldness generally is due to the failure of the hairs to be permitted to grow into terminal hairs, the large "hair" as laymen understand that term to be. Instead, the fine vellous hair that normally would grow into the terminal hair is essentially precluded from such growth. Said compound acts in the following manner. The smooth muscles in the small blood vessels in the papilla part of connective tissue of skin that supplies the hair follicle are relaxed, thereby increasing blood flow to the hair matrix leading to the maturation of fine hairs into terminal hairs. As a result, there is permitted the maturation of the fine hairs into terminal hairs as would be the case in a normal person without baldness.

EXAMPLE I

The compound 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is described in the literature, including Downing, U.S. patent 3,043,840 (1962), Irons et al., U.S. patent 3,164,588 (1965), de Stevens et al, U.S. patent 3,163,645 (1964), and Jones et al., U.S. patent 3,025,292.

The use of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic agent, but never as a topical medication.

Reference has been made herein to 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is to be understood that any derivatives and salt forms of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the

invention and may be used instead of the 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

As this compound has limited solubility in water but has solubility in ethanol, an ethanolic solution is contemplated as a preferred embodiment.

To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

The compound 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for treating baldness. To test the suitability of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Trial no.	Active Ingredient	Placebo
1	1	3
2	1	2
3	2	2
4	3	2
5	1	1
6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

A propylene glycol solution is prepared with 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 5% ethanolic solution previously described.

EXAMPLE II

The use of 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic and antihypertensive agent, but never as a topical medication.

Reference has been made herein to 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is to be understood that derivatives and salt forms of 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-

1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. The compound 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is disclosed in deStevens et al., Experientia, 16, 113 (1960). The compound has a solubility in water of 0.8 mg/ml at 25°C, and a solubility in ethanol of 21 mg/ml at 25°C.

To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

50 mg 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is dissolved in 1000 ml water to provide a solution for use in treatment of baldness. A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for treating baldness. To test the suitability of 6-chloro-3-

(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Trial no.	Active Ingredient	Placebo
1	1	3
2	1	2
3	3	2
4	3	2
5	1	1
6	1	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the previously described 5% ethanolic solution.

EXAMPLE III

The compound 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide is described in the literature. Reference has been made herein to 2-chloro-5-(1-hydroxy-3-oxo-

1-isoindolinyl)benzene sulfonamide. It is to be understood that any derivatives and salt forms of 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide are also contemplated within the scope of the invention and may be used instead of the 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide.

As this compound has limited solubility in water but has solubility in ethanol, an ethanolic solution is contemplated as a preferred embodiment.

To a graduated 1000 ml beaker there are added first 20 mg powdered 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert ...ng directions for the topical administration of 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide for alleviation of the effects of baldness.

The compound 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide was tested for treating baldness. To test the suitability of 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 2-chloro-5-

(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide.

Trial no.	Active Ingredient	Placebo
1	3	3
2	1	2
3	2	2
4	3	2
5	1	1
6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide in place of the 5% ethanolic solution.

EXAMPLE IV

Synthesis of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is disclosed in Holdrege et al., J. Am. Chem. Soc., 81, 4807 (1959); and Goldberg, U.S. patent 3,265,573 (1966).

The use of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic and antihypertensive agent, but never as a topical medication.

Reference has been made herein to 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-

sulfonamide 1,1-dioxide. It is to be understood that derivatives and salt forms of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

The compound is not soluble in water but is soluble in alcohols, making an ethanolic solution a preferred embodiment of the present invention.

To a graduated 1000 ml beaker there are added first 20 mg powdered 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

was tested for treating baldness. To test the suitability of 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Trial no.	Active Ingredient	Placebo
1	3	3
2	1	2
3	1	2
4	1	2
5	3	1
6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 95% ethanolic solution.

EXAMPLE V

Synthesis of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is disclosed in Close et al., J. Am. Chem. Soc., 82, 1132 (1960). The use of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic and antihypertensive agent, but never as a topical medication.

Reference has been made herein to 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is to be understood that any derivatives and salt forms of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

The compound 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is sparingly soluble in ethanol, and almost insoluble in water.

To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the above solution, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for treating baldness. To test the suitability of 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Trial no.	Active Ingredient	Placebo
1	1	3
2	3	2
3	2	2
4	2	2
5	3	1
6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-

7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 5% ethanolic solution.

EXAMPLE VI

Synthesis of 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is disclosed in McManus, U.S. Patent 3,009,911 (1961). The use of 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic and antihypertensive agent, but never as a topical medication.

Reference has been made herein to 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is to be understood that derivatives and salt forms of 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is desirable to include in any aqueous medium alkali metal carbanates or hydroxides because the compound 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is practically insolube in water without this adjustment.

To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed

together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

50 mg 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is dissolved in 1000 ml water having added thereto magnesium carbonate to provide a solution for use in treatment of baldness in accordance with this example.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

A propylene glycol solution is prepared with 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 95% ethanolic solution.

EXAMPLE VII

The compound 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is described in the literature, including Downing, U.S. patent 3,043,840 (1962), Irons et al., U.S. patent 3,164,588 (1965), de Stevens et al, U.S. patent 3,163,645 (1964), and Jones et al., U.S. patent 3,025,292.

The use of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is known as a diuretic agent, but never as a topical medication.

Reference has been made herein to 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is to be understood that any derivatives and salt forms of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide are also contemplated within the scope of the invention and may be used instead of the 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

As this compound has limited solubility in water but has solubility in ethanol, an ethanolic solution is contemplated as a preferred embodiment.

To a graduated 1000 ml beaker there are added first 20 mg powdered 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by addition of water to the 1000 ml mark. The resultant solution contains a two percent 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for treating baldness. To

test the suitability of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Trial no.	Active Ingredient	Placebo
1	2	3
2	2	2
3	2	2
4	3	2
5	1	1
6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 5% ethanolic solution.

EXAMPLE VIII

Testing of the compound 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is provided in this example. To a graduated 1000 ml beaker there are added first 20 mg powdered 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 55 ml 95% ethanol which are intimately mixed together, followed by

addition of water to the 1000 ml mark. The resultant solution contains a two percent 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in a 5% ethanolic solution suitable for topical application to the scalp of a bald patient for the treatment of baldness.

For the treatment of baldness, on a daily basis there is administered 2 cc to the scalp of said patient for the growth of hair on said bald spot. Administration is carried on twice a day, once in the morning after showering and once in the evening before retiring.

50 mg 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is dissolved in 1000 ml water having added thereto magnesium carbonate to provide a solution for use in treatment of baldness in accordance with this example.

A standard bottle for pharmaceutical liquids is filled with 200 ml of the solution of this example, and placed in a rectangular cardboard package together with a package insert giving directions for the topical administration of 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide for alleviation of the effects of baldness.

The compound 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was tested for treating baldness. To test the suitability of 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide as a treatment agent for baldness the following test was conducted. A total of 12 mouse trials were involved. A test was made for 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide on hairless weanling mice on a grading scale of no hair growth ("0"); sparse growth ("1"); fuzzy growth ("2"); and very fuzzy growth ("3"). Six different mice were tested for the compound 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-

sulfonamide 1,1-dioxide versus six placebo trials. In the following tabulation, "active ingredient" refers to the compound 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Trial no.	Active Ingredient	Placebo
1	2	3
2	2	2
3	2	2
4	3	2
5	1	1
6	3	1

With the placebo having only one trial hitting the 3 level and two with the 1 level, the trials for 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide show a superior result for the compound of this example versus the placebo.

A propylene glycol solution is prepared with 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide in place of the 95% ethanolic solution.

WHAT IS CLAIMED IS:

1. A method of enhancing growth of fine vellous hair into terminal hair in an least partially bald person which comprises topically applying to the scalp a compound selected from the group consisting of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide, 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide whereby the smooth muscles in the small blood vessels in the papilla part of connective tissue of skin that supplies the hair follicle is relaxed, thereby increasing blood flow to the hair matrix leading to the maturation of fine hairs into terminal hairs.

2. A method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 1, wherein said compound is applied from a topical solution containing at least about 0.01 weight percent said compound in a suitable carrier for said compound.

3. A method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 2, wherein said suitable carrier is propylene glycol.

4. A method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 2, wherein said suitable carrier is an ethanolic solution.

5. A method of permitting the normal growth of fine vellous hair into terminal hair in an least partially bald person in accordance with claim 2, wherein the solvent is a mixture of ethylene glycol and propylene glycol.

6. A method of claim 1 wherein said compound is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

7. A method of claim 1 wherein said compound is 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

8. A method of claim 1 wherein said compound is 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzene sulfonamide.

9. A method of claim 1 wherein said compound is 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

10. A method of claim 1 wherein said compound is 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

11. A method of claim 1 wherein said compound is 6-chloro-3,4-dihydro-2-methyl-3-{[(2,2,2-trifluoroethyl)thio]methyl}-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

12. A method of claim 1 wherein said compound is 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

13. A method of claim 1 wherein said compound is 3,4-dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

14. A topical medication for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises a baldness-reversing amount of a compound of claim in a form suitable for topical administration in a carrier therefor, said compound on continued application to said scalp effecting the growth of hair thereon.

15. A topical medication of claim 14 wherein said compound is present in an amount of at least about 0.01 weight percent in said suitable carrier.

16. A method for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises administering topically to said scalp a baldness-reversing amount of a compound of claim 1.

17. A kit containing a medication suitable for reversing the effects of baldness on the scalp of an at least partially bald subject which comprises a package containing:

(a) a container including a topical medication containing a compound of claim 1 for topical administration to the scalp of said subject; and

(b) directions for administration of said compound to said scalp for the reversal of the effects of baldness

said compound upon continued application to said scalp effecting the growth of hair thereon.

18. A kit of claim 17 wherein said compound in said container (a) includes a topical solution containing at least about 0.01 weight percent said compound in a carrier suitable therefor.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/01575

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 7/06; A 61 K 31/54; A 61 K 31/40

II. FIELDS SEARCHED

Minimum Documentation Searched †

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ‡

III. DOCUMENTS CONSIDERED TO BE RELEVANT §

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X,Y	The Merck Index, 10th edition, 1983, Merck & Co., Inc., (Rahway, N.J., US), see page 147, no. 1036; pages 305-306, no. 2143, page 310, no. 2171; pages 692-693, no. 4683; pages 694-695, no. 4695; page 863, no. 5883; page 1095, no. 7457; page 1376, no. 9437	14-18
X	US, A, 3476858 (NELSON et al.) 4 November 1968 see column 6, example 5	14-18
X	EP, A, 0125420 (BOEHRINGER INGELHEIM LTD) 21 November 1984 see page 11, lines 24-26	14-18
Y	EP, A, 0027655 (WELLA AG) 29 April 1981 see the whole document, in particular page 2, line 6 - page 3, line 11	14-18
Y	US, A, 4184039 (SOLDATI et al.) 15 January 1980 ./.	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21st August 1987	- 2 OCT 1987
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	L. ROSSI

Form PCT/ISA/210 (second sheet) (January 1985)

International Application No. PCT/US 87/01575

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	see the whole document --------	14-18

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 1-13 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv) Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the International application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 87/01575 (SA 17849)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 10/09/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 3476858	04/11/69	None		
EP-A- 0125420	21/11/84	AU-A-	2569684	20/09/84
		JP-A-	59176212	05/10/84
		CA-A-	1212329	07/10/86
		AU-B-	562929	25/06/87
EP-A- 0027655	29/04/81	DE-A-	2942666	07/05/81
		JP-A-	56065811	03/06/81
		AT-B-	E6464	15/03/84
US-A- 4184039	15/01/80	None		